

REMARKS

I. Overview

Claims 1-20 are pending. Claims 2 and 19 have been amended to improve clarity. The Office Action of September 19, 2006 indicates that claims 6, 9, and 15-17 are withdrawn from consideration as directed to non-elected species. The present response is an earnest effort to place all claims in proper form for immediate allowance. Reconsideration and passage to issuance is respectfully requested.

II. Priority

The Office Action indicates the prior-filed application, Application No. 60/395,763, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. § 112 for one or more claims of this application. In particular, the Office Action indicates that claims 1-14 and 18-20 are not entitled to the benefit of the prior application.

To be clear, the present application claims priority to three separate provisional patent applications. It is respectfully submitted that claims of this application are entitled to the benefit of one or more of the earlier filed applications.

III. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 2 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action indicates it is unclear what is being modified, the model of the organism or the organism itself and, it is unclear what the modification is. Claim 2 has been amended to clarify.

Claim 2 now requires "using the at least one candidate to genetically modify the organism." Thus, it should be clear that it is the organism itself which is modified, and that the modification is a genetic modification. Thus, it is respectfully submitted that this rejection should be withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph. The Office Action indicates that the specification, while being enabling for the formation of a bilevel optimization problem, does not reasonably provide enablement for the formation of any optimization problem. This rejection is respectfully traversed.

First it is observed that the specification describes the use of linear programming as one means to solve an optimization problem. The specification explains at paragraph [0038] that for every linear program problem (primal) there exists a unique optimization problem (dual) whose optimal objective value is equal to that of the primal problem. Paragraph [0042] and the equations following the paragraph illustrate a bi-level formulated optimization problem transformed into a single-level mixed integer linear programming problem. Thus, enablement is clearly provided for not just bi-level optimization problems, but also other types of optimization problems.

It is further observed that what is claimed in claim 1 is a "method for determining candidates for gene deletions and additions using a model of a metabolic network associated with an organism." The Office Action indicates that the formation of an optimization problem and concomitant mathematical statement and solution of the problem presents a complex, computational hurdle that remains to be overcome, citing the Papin et al., 5/2003, Trends in

Biochemical Sciences, 28(5):250-258, p. 256). However, the computational problem is not that the optimization problem cannot be formed or solved, the computational problem is solving such optimization problems in a desired amount of time or with a limited amount of computational resources. See e.g. paragraph [0038] describing a complex problem as "intractable". Thus, where time or computational resources are not constraints, or where the metabolic network is sufficiently small, there is no computational hurdle to overcome. Although the specific optimization problem formed and solved may be selected in part due to such constraints, doing so is certainly not necessary and no undue experimentation is required by one skilled in the art having the benefit of the application's disclosure.

Thus, the Office Action has failed to provide evidence or sound scientific reasoning to support the allegation that undue experimentation is required in order to practice claim within its full scope. It is respectfully submitted that the rejection must be withdrawn.

V. Claim Rejections Under 35 U.S.C. § 103

Claims 1-5, 7-8, 10-14, and 18-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Burgard et al. (Biotechnology and Bioengineering, 2001 74:364-375), in view of Yang et al. (Metabolic Engineering, 1999, 1:26-34) and further in view of Voit (Biotechnology and Bioengineering, 1992, 40:572-582). These rejections are respectfully traversed.

With respect to claim 1, claim 1 requires "forming an optimization problem that couples the at least one cellular objective with the bioengineering objective." Neither Burgard et al., nor Yang et al., nor Voit disclose this element. Nor do any of these references provide any motivation or suggestion to combine the references to provide this missing element. In fact, the Office Action does not even allege that any of the references discloses such a element. The

Office Action, page 7, merely indicates that "Burgard et al. teach a method of identifying gene candidates for deletion and addition by forming and solving an optimization problem that involves a bioengineering objective and a cellular objective", falling short of alleging that the required coupling takes place.

Burgard et al., on pages 369-371 discuss a gene knockout study which explores what is the smallest gene set capable of maximizing biomass production on glucose substrate and what is the maximum number of gene deletions from this set that still maintain a specified level of biomass production. Biomass production is one example of a cellular objective.

Separately, on pages 371-373, Burgard et al. discussed identifying mathematically optimal reaction pathways to recombine into the *E. coli* metabolic network to optimize amino acid formation for growth on glucose and acetate. Optimization of amino acid formation may be a bioengineering objective.

However, although Burgard et al. discusses cellular objectives and discusses bioengineering objectives, Burgard et al. certainly does not disclose forming and solving an optimization problem that couples at least one cellular objective with the bioengineering objective. Yang et al. is a 1992 reference which discusses the use of s-systems, for optimization of integrated biochemical networks. Yang et al does not discuss forming an optimization problem that couples at least one cellular objective with a bioengineering objective.

Voit discusses the use of multilevel programming in solving optimization problems, yet Voit does not disclose forming an optimization problem that couples at least one cellular objective with a bioengineering objective. Thus, there is no *prima facie* case of obviousness with respect to claim 1 as none of the prior art references disclose "forming an optimization problem that couples the at least one cellular objective with the bioengineering objective." Moreover,

there is no proper motivation or suggestion to combine such references to teach this missing element. Therefore the rejection to claim 1 must be withdrawn. As claims 2-5, 7-8, 10-14, 18 and 20 depend from claim 1, these rejections should also be withdrawn.

Independent claim 19 requires "forming an optimization problem that quantifies the cellular objective as an aggregate reaction flux and couples the at least one cellular objective with the bioengineering objective." The rejection to claim 19 should be withdrawn as neither Burgard et al. nor Yang et al. or Voit disclose this element, and as no proper motivation or suggestion to combine these references is provided.

The Office Action indicates that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the bilevel optimization of Voit in the method of Burgard et al. to develop the strain of *E. coli* that overproduce lactate as taught by Yang et al. and Voit to result in the instantly claimed invention, by Yang et al. because the organism, *E. coli*, is "extensively used in industry as a host for recombinant protein production (Yang et al., p. 26-27)" and by Voit because bacteria could be used to produce unnaturally high amounts of oxychemicals that can be used as alternative fuels (p. 579)" and recombinant protein production and would have reasonably expected success in view of the teachings of Burgard et al. and Voit. Even if the references are combined, there is no *prima facie* case of obviousness because none of the references disclose forming an optimization problem that couples at least one cellular objective with a bioengineering objective, and there is no proper motivation or suggestion to combine these references in a manner which would provide this missing element.

VI. Provisional Double Patenting, 35 U.S.C. § 101

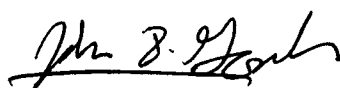
The Office Action indicates that claim 19 is provisionally rejected as claiming the same invention as that of claims 1-18 of co pending application no. 10/929,091. This rejection is respectfully traversed. In particular, claim 1 of the 10/929,091 application requires "identifying at least one stoichiometrically balanced pathway at least partially based on the reactions and a substrate to minimize a number of non-native functionalities in the production host." The other independent claims have similar limitations. The inclusion of such limitations do not result in coextensive scope with claim 19. Therefore this rejection should be withdrawn.

VII. Conclusion

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



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